REMARKS

The present Office Action addresses and rejects claims 48-69. Applicants respectfully request reconsideration of the present application in view of the following remarks.

The Invention

The instant invention is directed to a composition comprising a biocompatible substrate and a genetically altered chondrocyte. The genetically altered chondrocyte is capable of expressing a therapeutic agent in a target region associated with a disorder.

Independent claim 48 recites, *inter alia*, that the biocompatible substrate is *of a length in a range of about 10 cm to about 30 cm* and the genetically altered chondrocyte is *not used for tissue repair or construction*. Thus, the genetically altered chondrocyte functions to deliver the therapeutic agent at the ectopic site instead of the normal function which is to repair or replace surrounding tissue. Additionally, the biocompatible substrate size recitation reinforces the utility of the composition at an *ectopic site* where the altered chondrocyte is not used for *tissue repair or construction*.

Independent claim 60 recites, *inter alia*, that the genetically altered chondrocyte is *not used for tissue repair or construction* and the therapeutic agent expressed by the genetically altered chondrocyte is selected from the group consisting of *Erythropoietin protein and Erythropoietin mimetibody*.

None of the cited references disclose the claimed composition either individually or in combination. Therefore, claims 48 and 60, as well as their dependent claims, are novel over the cited references.

Rejections Pursuant to 35 U.S.C. §103

Glorioso

Claims 48-51 and 54-56 stand rejected pursuant to 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,413,511 of Glorioso et al. ("Glorioso").

Glorioso discloses a method for introducing a polynucleotide encoding for a polypeptide into either chondrocytes or synovial cells for *alleviating pathologies of the joint*. In fact, the

main focus of Glorioso is on the use of polypeptide modified chondrocytes encoding for a non-native polypeptide for the treatment of *joint pathologies*. Nowhere does Glorioso disclose compositions comprising a *biocompatible substrate of a length in a range of about 10 cm to about 30 cm* and a genetically altered chondrocyte that *is not used for tissue repair or construction*, much less compositions wherein the genetically altered chondrocyte expresses a therapeutic agent in an *ectopic site*.

The Examiner admits that Glorioso "does not teach use of a substrate having a length of about 10 cm to 30 cm." The Examiner argues that "[i]t would have been obvious to make a large 10 cm long implant to accommodate a larger lesion, to provide a large enough implant that a piece can be cut to fit an implant site, or to cut multiple implants from the same larger substrate" on the basis that "Glorioso does teach making a larger than necessary biocompatible substrate and cutting the substrate to fit the implant site." The Examiner is incorrect. Although Glorioso discloses that a gel that can be "cut to an appropriate size," this disclosure provides no teaching or suggestion regarding the claimed length range.

In particular, Glorioso merely discloses that "[t]he chondrocyte/collagen gel was evacuated from the microfuge tube into a sterile Petri dish and cut to an appropriate size with a scalpel." Glorioso at col. 46, lines 41-43. Thus, the only teaching or suggestion regarding the size of the gel is that it should be cut to an *appropriate size*. Glorioso is directed to use of the chondrocyte/collagen gel in a joint for repair of articular defects. These defects are many times smaller than the claimed lengths. In fact, the size of the defect for which the chondrocyte/collagen gel is "cut to an appropriate size" is a "large 6 mm x 3 mm x 3 mm full-thickness medial femoral articular cartilage defect." Glorioso at col. 46, lines 39-41. Thus, a "large" defect according to Glorioso is only 6 mm long. Therefore, Glorioso would provide no teaching or suggestion to one of ordinary skill in the art to use a substrate many times larger than that disclosed by Glorioso. It is only with the benefit of hindsight and with Applicants' specification and claims as a road map that the Examiner comes to the conclusion that the claimed size range would have been obvious. Therefore, contrary to the Examiner's assertions, it would not have been obvious in light of Glorioso to make a "large 10 cm long implant."

Accordingly, claim 48, as well as claims 49-51 and 54-56 which depend therefrom, distinguish over Glorioso and represent allowable subject matter.

Glorioso in view of Bartholomew

Claims 52-53 and claims 60-64 and 69 stand rejected pursuant to 35 U.S.C. 103(a) as being unpatentable over Glorioso in view of Bartholomew et al. (Human Gene Therapy, 2001, 12:1527-1541) ("Bartholomew").

At the outset, claims 52-53 depend from claim 48 and therefore distinguish over Glorioso for at least the reasons discussed above with respect to claim 48. Bartholomew fails to remedy the deficiencies of Glorioso with respect to a *biocompatible substrate of a length in a range of about 10 cm to about 30 cm* or a genetically altered chondrocyte that *is not used for tissue repair or construction*, much less compositions wherein the genetically altered chondrocyte expresses a therapeutic agent in an *ectopic site*.

Bartholomew discloses the use of immunoisolatory devices (IID's) for aiding modified *mesenchymal stem cells* expressing human erythropoietin (EPO) after implantation into baboons. There is no teaching or suggestion in Bartholomew of a composition using a *biocompatible substrate* in their implants, let alone a biocompatible substrate *of a length in a range of about 10 cm to about 30 cm*. Nor is there any teaching of a genetically altered *chondrocyte*, much less the ability of the altered cultured chondrocyte to express the therapeutic agent when delivered at an ectopic site and not used for tissue repair or construction. Neither Glorioso nor Bartholomew teach or suggest a composition with a biocompatible substrate *of a length in a range of about 10 cm to about 30 cm*. Nor would it have been obvious to one of ordinary skill in the art to add such a biocompatible substrate to the combination since Glorioso does not mention any such use and Bartholomew uses IID's to encompass their implants.

Furthermore, the combination of Glorioso and Bartholomew does not teach a genetically altered *chondrocyte,* cultured and modified to express a therapeutic agent. The cells used in Bartholomew are *mesenchymal stem cells*, whereas in the current application, a *chondrocyte* is genetically altered to express a therapeutic agent. Stem cells behave, interact and respond differently than differentiated cells, such as chondrocytes.

In particular, applications and techniques performed on a stem cell, such as those taught by Bartholomew are not predictably applicable or obvious for use with polypeptide introduced chondrocytes, as in Glorioso. Accordingly, combining the teachings of Bartholomew with the

polypeptide-introduced chondrocytes of Glorioso would not have yielded predictable results to one of ordinary skill in the art and would therefore not have been obvious. Once again, it is only with the benefit of hindsight and with Applicants specification and claims as a road map that the Examiner comes to the conclusion that one of ordinary skill in the art would practice the production of a composition having a genetically altered chondrocyte cultured and modified to express an Erythropoietin protein or Erythropoietin mimetibody.

Accordingly, claims 52-53 and claims 60-64 and 69 distinguish over Glorioso and Bartholomew, alone or in combination, and represent allowable subject matter.

Glorioso in view of Okada

Claims 57-59 and 65-67 stand rejected pursuant to 35 U.S.C. 103(a) as being unpatentable over Glorioso, in view of Okada (Biol. Pharm. Bull. 1997, Vol. 20, No. 3, p 255-258) ("Okada").

At the outset, claims 57-59 and 65-67 depend from claims 48 and 60, respectively and therefore distinguish over Glorioso for at least the reasons discussed above with respect to claims 48 and 60. Okada fails to remedy the deficiencies of Glorioso with respect to a *biocompatible substrate of a length in a range of about 10 cm to about 30 cm* or a genetically altered chondrocyte that *is not used for tissue repair or construction*, much less compositions wherein the genetically altered chondrocyte expresses a therapeutic agent in an *ectopic site*.

Okada discloses encapsulating SK2 hybridoma cells that secrete anti-hIL6 monoclonal antibodies to suppress IgG1 plasmocytosis in transgenic mice. There is no teaching or suggestion in Okada regarding the use of a *genetically altered chondrocyte* in their implants, much less a composition comprising a biocompatible substrate *of a length in a range of about 10 cm to about 30 cm* and a *genetically altered chondrocyte* that expresses a therapeutic agent at an ectopic site.

Just as the mesenchymal stem cells of Bartholomew, SK2 hybridoma cells are a very different cell type than *chondrocytes*. SK2 hybridoma cells were made from an anti-hIL-6 antibody secreting B cell that was fused with a myeloma cell to produce the anti-hIL-6 hybridoma cell line. Applications and techniques performed on a hybridoma cell line, such as those taught by Okada are not obvious or predictably applicable to polypeptide introduced

chondrocytes, as in Glorioso. Thus, combining the teachings of Okada with the polypeptide introduced chondrocytes of Glorioso would not have been obvious to one of ordinary skill in the art.

Accordingly, claims 57-59 and 65-67 distinguish over the combination of Glorioso in view of Okada and represent allowable subject matter.

Conclusion

Applicants submit that all claims are in condition for allowance, and allowance thereof is respectfully requested. If the Examiner believes that an interview would facilitate the resolution of any outstanding issues, the Examiner is kindly requested to contact the undersigned.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 141449, under Order No. 22956-225.

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Respectfully submitted,

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